

In the Claims:

1-27. (Canceled)

28. (Currently Amended) A method of designing amino acid sequences of variable domains of a humanized monoclonal antibody ~~to be humanized~~ comprising:

(a) determining residue identities between the amino acid sequences of the light and heavy chain a variable domains of a monoclonal antibody to be humanized and corresponding light and heavy chain variable domains of two or more human ~~monoclonal~~ antibodies;

(b) selecting from said corresponding variable domains of two or more human antibodies, at least one human antibody for the framework regions from two or more of said corresponding variable domains of light chains and at least one human antibody for the framework regions of heavy chains wherein ~~each the human antibody for the framework regions of the light chains is different from the human antibody for the framework region of the heavy chains and~~ framework regions of the heavy chain ~~have~~ have a sequence identity of approximately 75.0 to 92.3% at least 62.5% and framework regions of the light chain have a sequence identity of at least 69% to the corresponding framework regions in the monoclonal antibody ~~to be humanized~~;

(c) incorporating the framework regions selected in step (b) with the complementarity determining regions of the monoclonal antibody to be humanized to design a humanized variable domain, ~~wherein at least two of said framework regions are from different human monoclonal antibodies~~;

(d) retaining selected amino acid residues from the framework regions of the monoclonal antibody to be humanized in the corresponding framework regions of the humanized variable domain if one or more of said selected amino acids are predicted to have contacts with said complementarity determining regions affecting the affinity and specificity of the resultant humanized monoclonal antibody; and

(e) obtaining amino acid sequences of the variable domains of the light and heavy chain regions of the resultant humanized monoclonal antibody.

29. (Currently Amended) The method according to claim 28, wherein at least three of said framework regions are from different human ~~monoclonal~~ antibodies.

30. (Currently Amended) The method according to claim 28, wherein said heavy chain framework regions are from the heavy chain regions of at least two different human ~~monoclonal~~ antibodies.

31. (Currently amended) The method according to claim 28, wherein said selected amino acid residues of step (d) are within a 4.5 Angstrom radius of any ~~all~~ atoms within a ~~each~~ complementarity determining regions of the light or ~~and~~ heavy chain of the resultant humanized monoclonal antibody.

32. (Previously presented) A method of producing a humanized monoclonal antibody designed according to the method of claim 28, comprising the additional steps of:

- (f) preparing a DNA sequence encoding the variable domains of the resultant humanized monoclonal antibody based upon the designed amino acid sequence;
- (g) operably incorporating the DNA sequences into at least one vector comprising the constant domains of the light and heavy chain regions;
- (h) introducing the vector into a cell; and
- (i) culturing the cell under conditions to produce the humanized monoclonal antibody.

33. (New) A method of designing amino acid sequences of variable domains of a humanized monoclonal antibody comprising:

- (a) determining residue identities between the amino acid sequences of variable domains of a monoclonal antibody to be humanized and corresponding variable domains of two or more human antibodies;
- (b) selecting from said corresponding variable domains of two or more human antibodies, at least one human antibody for the framework regions of the light chain and at least one different human antibody for the framework regions of the heavy chain;
- (c) incorporating the framework regions selected in step (b) with complementarity determining regions of the monoclonal antibody to be humanized to design a humanized light chain variable domain and a humanized heavy chain variable domain;

(d) retaining selected amino acid residues from the framework regions of the monoclonal antibody to be humanized in the corresponding framework regions of the humanized variable domain if one or more of said selected amino acids are predicted to have contacts with said complementarity determining regions affecting the affinity and specificity of the resultant humanized monoclonal antibody; and

(e) obtaining amino acid sequences of the variable domains of the light and heavy chain regions of the resultant humanized monoclonal antibody.

34. (New) The method according to claim 33, wherein said framework region sequences are selected from at least three different human antibodies.

35. (New) The method according to claim 33, wherein said heavy chain framework regions are selected from the heavy chain regions of at least two different human antibodies.

36. (New) The method according to claim 33, wherein said selected amino acid residues of step (d) are within a 4.5 Angstrom radius of atoms within a complementarity determining region of the light or heavy chain of the resultant humanized monoclonal antibody.

37. (New) A method of producing a humanized monoclonal antibody designed according to the method of claim 33, comprising the additional steps of:

(f) preparing a DNA sequence encoding the variable domains of the resultant humanized monoclonal antibody based upon the designed amino acid sequence;

(g) operably incorporating the DNA sequences into at least one vector comprising the constant domains of the light and heavy chain regions;

(h) introducing the vector into a cell; and

(i) culturing the cell under conditions to produce the humanized monoclonal antibody.